DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1141 Central Parkway
Cincinnati, OH 45202

August 12, 1997

**WARNING LETTER**
**CIN-WL-97-416**

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Ola Andersson, President
Pharmacia Hepar, Inc.
160 Industrial Drive
Franklin, OH 45005

Dear Mr. Andersson:

During an April 2 through May 15, 1997 inspection of your bulk Heparin manufacturing facility, located at the above address, our investigators documented significant deviations from the current U.S. good manufacturing practice for bulk pharmaceutical chemicals. These deviations cause these bulk drug substances to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice (cGMP). No distinction is made between bulk drug substances and finished pharmaceuticals, and failure of either to comply with cGMP constitutes a failure to comply with the requirements of the Act.

These deviations include the following:

1) Failure to establish appropriate cleaning procedures for final production (post-final filtration) equipment in that soft water, which has not been shown to be pyrogen-free, is used for washing equipment surfaces.

We reviewed your response to observation one of the FDA-483 Inspectional Observations and acknowledge your commitment to change your equipment cleaning procedure to use Water for Injection (WFI) instead of soft water to control endotoxin. The correction appears to be appropriate except that we are concerned about the time frame you propose to complete the correction (first quarter of 1998). Please provide an interim plan that you will use to control endotoxin prior to

implementation of a WFI system in 1998. All corrections will be verified at reinspection.

We feel application of potable water specifications to soft water is not appropriate since soft water may introduce pathogens or endotoxin into the product.

We are concerned because your soft water contributes microbial load to your potable water; you do not test your soft water for endotoxin levels; you do not gram stain or identify the bacteria present in your soft water; the soft water is used to clean production equipment that contacts final product; and, your active pharmaceutical ingredients are distributed for use by parenteral pharmaceutical manufacturers.

We expect active pharmaceutical manufacturers to control endotoxin in their process where products are used to manufacture parenteral pharmaceuticals.

We recommend that you assess the areas where soft water is used throughout your process and use water low in endotoxin in areas where the soft water may add endotoxin to the product.

2) Failure to adequately investigate out-of-specification LAL endotoxin test failures, when there is no evidence of laboratory error, in that investigations do not extend to examination of environmental bioburden and water systems. For example:

   a) In following up on out-of-specification LAL results for Heparin Sodium USP lot PM 593-97, your firm released the drug based on results of retesting alone without further investigation to identify possible causes, such as environmental bioburden, water systems, etc.

   b) In following up on out-of-specification LAL results for Topical Heparin, lot TH 197-96 and TH 198-96, your investigation did not attempt to determine whether the results may have been caused by high bacterial counts in the water system.

We reviewed your response to FDA-483 observation number two and SOP 40-201, Microbiological Retest Procedure For Final Products, that you submitted with your response. The SOP allows release of a batch on retest results alone. There should be

a thorough investigation to determine if there is sufficient basis to invalidate a test result and support accepting a retest result. Your assertion is incorrect that the FDA Guideline on Validation of the Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices allows for retesting to invalidate original test results. The retest is to insure that the test itself was not contaminated.

Endotoxin retesting is acceptable provided the cause of the initial test failure is known, thereby invalidating the original results i.e. investigation reveals that the test system was compromised. It cannot be assumed that the initial endotoxin test failure is a false positive. This conclusion must be justified by sufficient documented investigation.

Your investigation of Heparin Sodium U.S.P. lot PM 593-97 determined that there were no errors found in the test. Additionally, retesting alone does not assure that Heparin Sodium U.S.P. lot PM 593-97 meets U.S.P. specifications for endotoxin limits. There should be an adequate investigation as to the cause of the out of specification result.

3) Failure to adequately control environmental conditions that may impact on product quality in that investigations into high viable particulate air contamination are not always immediately acted upon and remedial action taken.

Lack of adequate controls over air contaminants is evidenced by the lack of follow-up, documented investigation and remedial action taken in instances where viable air count limits were exceeded in purification rooms 213 and 216.

Your response fails to specify any corrections taken to assure that the viable air count consistently meets specifications.

4) Failure to establish appropriate testing of filtration systems in that the [redacted] filter used in the final filtration of Heparin Sodium USP is not post-filtration integrity tested each time a new batch is produced.

Your response to this issue appears acceptable; however, we request you provide your corrected SOP in your written response to this communication. This issue will

be verified upon reinspection.

5) Failure to employ appropriate filtration systems in that the [redacted] filters used for the final purification of low molecular weight Heparin are not integrity testable.

Your response to this issue appears acceptable due to the infrequency with which you manufacture low molecular weight heparin. We do expect, however, product testing and data evaluation to be much more extensive than the usual situation where more reliance would be placed on prospective validation.

6) Failure to adequately monitor and control microbial conditions during processing in that timely investigations were not conducted into elevated CFU's in the soft water system, and there are no established limits or no mechanism which would initiate a QA investigation into such matters.

An investigation report regarding high CFU's encountered in the soft water system in October 1996 was not concluded and written until seven months later, on 5/5/97. This soft water is significant because it is used both for dilution of in-process product immediately prior to the purification steps, and is used for washing and rinsing equipment used after the final product filtration.

We have reviewed your bacterial endotoxin test records for Heparin Sodium U.S.P. and Topical Heparin batches and note that there appears to be no negative control run with each bacterial endotoxin test run. Also we did not find that a standard series was run when samples were retested. Please explain your rationale for not using a negative control or running a standard series if such is the case.

We also note that you did not retest Heparin Sodium U.S.P. lot PM 593-97 until two days after the initial failing test. Endotoxin has an affinity for glass surfaces. Please provide validation which addresses the change in sample conditions that occur over time. Endotoxin retest procedures should incorporate measures to assure that conditions of the original sample, upon resampling, are controlled to provide reliable results.

We have additional concerns regarding validation of your manufacturing process. Batches that fail to meet endotoxin limits are evidence that the manufacturing

process has not been validated to consistently produce product of predetermined quality. We are concerned that you rely on end product testing to release batches of product with endotoxin levels of not more than [redacted]. Please provide any validation data generated by your firm that supports the specification of not more than [redacted] endotoxin limit for Heparin Sodium.

The above enumeration of deficiencies should not be construed as an all inclusive list of violations which may be in existence concerning your drug product. It is your responsibility to ensure that all requirements of the Federal Food, Drug, and Cosmetic Act and regulations promulgated thereunder are being met. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We request that you take prompt action to correct these violations. Failure to achieve prompt corrections may result in enforcement action being initiated by FDA without further notice. These include seizure and/or injunction.

Please advise us in writing within fifteen (15) working days after receipt of this letter of the specific actions you have taken to correct the violations. Your response should include: (1) each step taken or those that will be taken to completely correct the current violations; (2) the time within which corrections will be completed; (3) any reason why the corrective action is not completed within the response time; and (4) any documentation necessary to indicate correction has been achieved.

Your reply should be sent to the Food and Drug Administration, 1141 Central Parkway, Cincinnati, Ohio 45202 to the attention of Charles S. Price, Compliance Officer.

Sincerely,

Diana J. Kolaitis
District Director
Cincinnati District

HFR-MA440:CSPrice:Hepar.wl

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